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(71) Applicant: **UNILEVER PLC**  
Unilever House Blackfriars P.O. Box 68  
London EC4P 4BQ(GB)

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(71) Applicant: **UNILEVER NV**  
Burgemeester s'Jacobplein 1 P.O. Box 760  
NL-3000 DK Rotterdam(NL)

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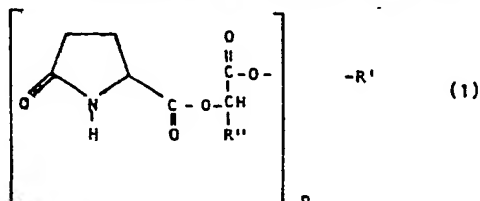
(72) Inventor: **Black, John Gordon**  
48 Orchard Lane  
Harrold Bedford, MK43 7BP(GB)

(72) Inventor: **Scott, Ian Richard**  
6 Hoyleke  
Wellingborough Northamptonshire, NN8 3NZ(GB)

(74) Representative: **Tonge, Robert James et al,**  
**UNILEVER PLC Patents Division** P.O. Box 68 Unilever  
House  
London EC4P 4BQ(GB)

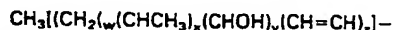
(84) **Pyroglutamic acid esters, their synthesis and use in topical products.**

(57) Esters of pyroglutamic acid having the structure:



when the subgrouping. (CH=CH) is present, then the total number of carbon atoms in said grouping will be from 16 to 22. Synthesis, and uses of the said esters in topical compositions are also provided.

where R' and R'' are the same or different and are each represented by H or the grouping



where

- n is an integer of from 1 to 3
- w is zero, or an integer of from 1 to 21
- x is zero, or an integer of from 1 to 4
- y is zero, or an integer of from 1 to 2
- z is zero, or an integer of from 1 to 4

provided that the total number of of carbon atoms in each of said grouping will not exceed 22; and provided also that

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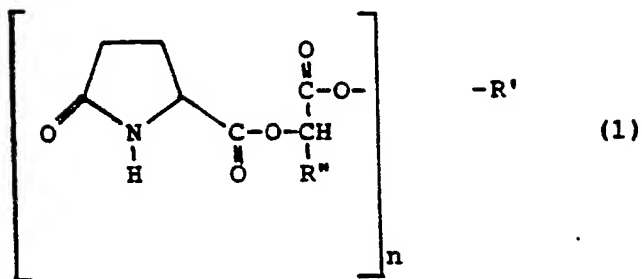
PYROGLUTAMIC ACID ESTERS, THEIR SYNTHESIS  
AND USE IN TOPICAL PRODUCTS

5       The invention relates to esters of pyroglutamic acid,  
their synthesis and their use in products for topical  
application to human skin as precursors of pyroglutamic  
acid.

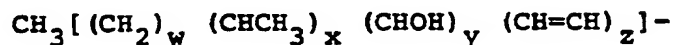
COMPOUNDS PER SE

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Accordingly the invention provides esters of  
pyroglutamic acid having the structure:



where R' and R'' are the same or different and are each represented by H or the grouping:



where n is an integer of from 1 to 3

w is zero, or an integer of from 1 to 21

x is zero, or an integer of from 1 to 4

y is zero, or an integer of from 1 to 2

z is zero, or an integer of from 1 to 4

provided that the total number of carbon atoms in each of said grouping will not exceed 22;

and provided also that when the subgrouping (CH=CH) is present, then the total number of carbon atoms in the said grouping will be from 16 to 22.

Examples of the grouping:



methyl

ethyl

propyl

iso-propyl

butyl

iso-butyl

tert-butyl  
valeryl  
iso-valeryl  
caproyl  
5 heptyl  
caprylyl  
capryl  
lauryl  
myristyl  
10 palmityl  
stearyl  
arachidyl  
behenyl  
hydroxy methyl  
15 2-hydroxy ethyl  
2-hydroxy propyl  
3-hydroxy propyl  
2-hydroxy butyl  
3-hydroxy butyl  
20 4-hydroxy butyl  
5-hydroxy valeryl  
6-hydroxy caproyl  
2,3-dihydroxy propyl  
2,3-dihydroxy butyl  
25 12-hydroxy stearyl  
linoleoyl  
linolenoyl  
arachidonoyl

30 It is to be understood that the above list is not exhaustive, there being many other examples of alkyl or substituted alkyl radicals expressed by the above generic grouping.

35 Specific examples of esters of pyroglutamic acid are:

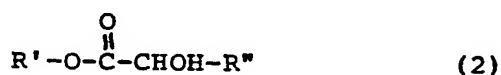
2-pyroglutamyl propionic acid  
methyl-2-pyroglutamyl acetate  
ethyl-2-pyroglutamyl propionate  
ethyl-2-pyroglutamyl n-butyrate  
5 ethyl-2-pyroglutamyl n-valerate  
ethyl-2-pyroglutamyl n-caproate  
ethyl-2-pyroglutamyl n-heptylate  
ethyl-2-pyroglutamyl n-caprylate  
ethyl-2-pyroglutamyl n-pelargonate  
10 ethyl-2-pyroglutamyl-3-hydroxybutyrate  
iso-propyl-2-pyroglutamyl propionate  
iso-propyl-2-pyroglutamyl n-caprylate  
n-propyl-2-pyroglutamyl propionate  
n-propyl-2-pyroglutamyl n-caprylate  
15 glyceryl mono(2-pyroglutamyl n-caprylate)  
glyceryl mono(2-pyroglutamyl propionate)  
glyceryl di(2-pyroglutamyl propionate)  
lauryl-2-pyroglutamyl n-caprylate  
stearyl-2-pyroglutamyl n-caprylate  
20 stearyl-2-pyroglutamyl propionate  
12-hydroxystearyl-2-pyroglutamyl propionate  
stearyl-2-pyroglutamyl stearate  
palmityl-2-pyroglutamyl propionate  
linoleoyl-2-pyroglutamyl propionate, and  
25 linoleoyl-2-pyroglutamyl n-caprylate.

It is to be understood that the above list of  
specific examples of esters of pyroglutamic acid is not  
exhaustive, there being many other examples expressed by  
30 the generic structure of these esters.

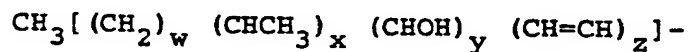
SYNTHESIS OF COMPOUNDS PER SE

The invention also provides a process for the synthesis of esters of 2-pyroglutamic acid which comprises the steps of:

- (i) reacting pyroglutamic acid with an acid ester having the structure:



where R' and R'' are the same or different and are each represented by H or the grouping:



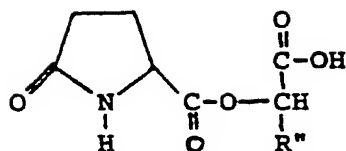
where w is zero, or an integer of from 1 to 21  
 x is zero, or an integer of from 1 to 4  
 y is zero, or an integer of from 1 to 2  
 z is zero, or an integer of from 1 to 4

provided that the total number of carbon atoms in each of said grouping will not exceed 22;

and provided also that when the subgrouping (CH=CH) is present, then the total number of carbon atoms in the said grouping will be from 16 to 22; and

- (ii) isolating the ester of pyroglutamic acid so obtained.

It will be appreciated that when R' in the above structure is H, then the product of step (i) in the above process will be an acid having the structure:



(3)

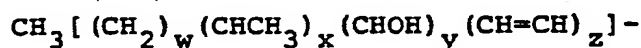
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It will then be necessary to condense this acid (3) with an alcohol having the structure:

10



where  $R'$  is represented by the grouping

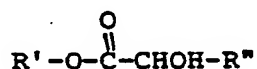


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in order to obtain the ester of pyroglutamic acid according to the invention having the structure (1).

20

Pyroglutamic acid and the acid or ester having the structure:



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can be reacted in the dry state by heating the mixture, preferably at a pressure of less than that of atmospheric pressure. It may, however, be more convenient to react pyroglutamic acid and the ester in the presence of an organic solvent and/or a drying agent.

30

This aspect of the invention is illustrated by the following examples.

Example 1

Synthesis of ethyl-2-pyroglutamyl propionate

5        Ethyl 2-pyroglutamyl propionate was prepared on a  
small scale by refluxing tritiated pyroglutamic acid with  
a 10 to 20 molar excess of ethyl 2-hydroxy propionate in  
xylene. Anhydrous magnesium sulphate was added to remove  
water. After 48 hours, volatile fractions were removed  
10 by rotary evaporation and ethyl 2-pyroglutamyl propionate  
was isolated by thin layer chromatography on silica gel H.  
The structure of the isolated ester of pyroglutamic acid  
was confirmed by mass spectrometry and its radio chemical  
purity by thin layer chromatography.

15

Example 2

Synthesis of ethyl-2-pyroglutamyl n-valerate

20        The procedure of Example 1 was repeated except that  
the ester employed was ethyl-2-hydroxy valerate.

Example 3

25        Synthesis of ethyl-2-pyroglutamyl n-caproate

The procedure of Example 1 was repeated except that  
the ester employed was ethyl-2-hydroxy caproate.

30

Example 4

Synthesis of ethyl-2-pyroglutamyl n-caprylate

35        The procedure of Example 1 was repeated except that  
the ester employed was ethyl-2-hydroxy caprylate.

Example 5

Synthesis of iso-propyl-2-pyroglutamyl propionate

5           2 moles of iso-propyl lactate were refluxed with 1  
mole of pyroglutamic acid in toluene with a Dean-Stark  
water entrainer for 72 hours. The reaction mix was  
cooled, filtered and rotary evaporated to leave an  
involatile oil containing the ester of pyroglutamic acid.

10

iso-Propyl-2-pyroglutamyl propionate was isolated by  
preparative scale high performance liquid chromatography  
using a hexane:ethanol gradient on a normal phase silica  
column. Its purity was confirmed by analytical high  
15 performance liquid chromatography and its structure by  
mass spectrometry.

Example 6

20           Synthesis of iso-propyl-2-pyroglutamyl n-butyrate

The procedure described in Example 5 can be repeated  
using iso-propyl-2-hydroxy n-butyrate as the ester  
instead of iso-propyl lactate.

25

Example 7

Synthesis of iso-propyl-2-pyroglutamyl n-caprylate

30           The procedure described in Example 5 was repeated  
except that the ester employed was iso-propyl-2-hydroxy  
n-caprylate.

Example 8

Synthesis of glyceryl mono-(2-pyroglutamyl n-caprylate)

5        3g of pyroglutamic acid was mixed with 3g of  
2-hydroxy caprylic acid and heated at from 140° to 150°C  
for three hours under 20mm pressure. The resulting  
2-pyroglutamyl n-caprylic acid was partially purified by  
10       extraction with ethyl ether followed by separation with  
petroleum ether (boiling point 40°-60°C). The ester  
concentrated in the lower phase was dried in a stream of  
nitrogen.

15       An excess of glycerol was added to the dried  
2-pyroglutamyl n-caprylic acid, heated at from 140° to  
150°C for 3 hours at 20mm pressure. The reaction mixture  
was cooled, extracted with 50% hexane, 50% ethanol and  
separated by preparative high performance liquid  
20       chromatography using a normal phase silica column and a  
gradient of hexane/ethanol. The isolated glyceryl  
mono-(2-pyroglutamyl n-caprylate) was checked for purity  
by analytical high performance liquid chromatography and  
for structure by mass spectrometry.

25       Example 9

Synthesis of lauryl-2-pyroglutamyl n-caprylate

30       The procedure as described in Example 8 was repeated  
except that in place of glycerol, lauryl alcohol was used.

Example 10

Synthesis of stearyl-2-pyroglutamyl n-caprylate

35       The procedure as described in Example 8 was repeated  
except that in place of glycerol, stearyl alcohol was used.

Example 11Alternative synthesis of ethyl-2-pyroglutamyl propionate

- 5        A mixture of 500g pyroglutamic acid, 1,000ml ethyl  
2-hydroxy propionate (ethyl lactate) and 1000 ml toluene  
were refluxed in a Dean-Stark apparatus for 48 hours.  
Toluene and excess ethyl lactate were then removed by  
rotary evaporation and the residue distilled under vacuum  
10    (<0.5 mm Hg). The initial distillate contained residual  
ethyl lactate and ethyl pyroglutamic acid as a byproduct.  
The final distillate, a slightly yellow viscous liquid,  
was pure ethyl-2-pyroglutamyl propionate.
- 15        In some of the foregoing examples, tritiated  
pyroglutamic acid was employed as one of the starting  
materials to confirm the purity of the isolated  
pyroglutamyl ester and to enable the fate of the tritiated  
ester of pyroglutamic acid to be ascertained when it is  
20    applied to skin, by locating tritiated pyroglutamic acid  
resulting from skin enzyme activity.

TOPICAL COMPOSITIONS

- 25        The invention further provides a composition for  
topical application to human skin which comprises an  
effective amount of from 0.01 to 99% by weight of an ester  
of pyroglutamic acid as herein defined together with a  
physiologically and cosmetically acceptable diluent.  
30    These compositions preferably comprise from 0.1 to 20%,  
most preferably from 0.5 to 5% by weight of the ester.

The esters of pyroglutamic acid are those as defined herein. The preferred esters for use in topical compositions according to the invention are:

- 5           2-pyroglutamyl propionic acid
- methyl-2-pyroglutamyl acetate
- ethyl-2-pyroglutamyl propionate
- ethyl-2-pyroglutamyl n-butyrate
- ethyl-2-pyroglutamyl n-valerate
- 10          ethyl-2-pyroglutamyl n-caproate
- ethyl-2-pyroglutamyl n-heptylate
- ethyl-2-pyroglutamyl n-caprylate
- ethyl-2-pyroglutamyl n-pelargonate
- ethyl-2-pyroglutamyl-3-hydroxybutyrate
- 15          iso-propyl-2-pyroglutamyl propionate
- iso-propyl-2-pyroglutamyl n-caprylate
- n-propyl-2-pyroglutamyl propionate
- n-propyl-2-pyroglutamyl n-caprylate
- glyceryl mono(2-pyroglutamyl n-caprylate)
- 20          glyceryl mono(2-pyroglutamyl propionate)
- glyceryl di(2-pyroglutamyl propionate)
- lauryl-2-pyroglutamyl n-caprylate
- stearyl-2-pyroglutamyl n-caprylate
- stearyl-2-pyroglutamyl propionate
- 25          12-hydroxystearyl-2-pyroglutamyl propionate
- stearyl-2-pyroglutamyl stearate
- palmityl-2-pyroglutamyl propionate
- linoleoyl-2-pyroglutamyl propionate, and
- linoleoyl-2-pyroglutamyl n-caprylate.

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The physiologically and cosmetically acceptable diluent can be water, physiological saline or any suitable organic solvent in which the ester is soluble or dispersible.

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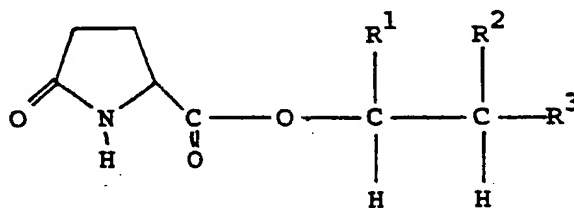
The composition can be a simple solution or dispersion or a gel or a cream.

The composition according to the invention can be applied topically to human skin in order to moisturise the skin and to leave it in a soft supple condition. The composition is accordingly particularly beneficial in remoisturising dry skin or for the treatment of chapped or detergent-damaged skin. The composition can also be employed in the topical treatment of acne comedones, pimples and spots, and in the topical treatment of ichthyosis, hyperkeratosis and psoriasis, and also for the topical treatment of sunburn.

In Japanese patent KOKAI 48-82046, published November 1973, moisturising and softening compositions are disclosed, these compositions containing as effective constituents pyrrolidone carboxylates represented by the following formula:

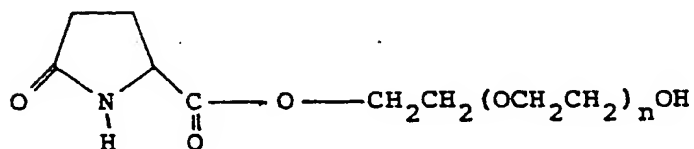
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25



or

30



35

where  $R^1$  is H,  $CH_3$  or  $CH_2OH$

$R^2$  is H or OH

$R^3$  is  $H_1$ ,  $CH_3$ ,  $CH_2OH$ ,  $CH_2CH_3$ ,  $CH(OH)CH_3$   
or  $CH_2CH_2OH$

n is the integer 1 or 2; and

the total number of carbon atoms in  $R^1$  and  $R^3$  is 1 or 2, and

the total of OH groups is 1 or 2.

#### MODE OF ACTION OF THE ESTERS

Pyroglutamic acid (also known as 2-pyrrolidone-5-carboxylic acid) is the principal ingredient of the "natural moisturising factor" that enables the stratum corneum of the skin to maintain a high water content despite low external humidity. Pyroglutamic acid applied topically to the skin has a temporary moisturising effect but it is easily washed away and gives no long term skin benefit.

The esters of pyroglutamic acid according to the invention are analogues of naturally occurring n-terminal pyroglutamic acid peptides. These naturally occurring peptides are substrates for the enzyme pyroglutamic acid peptidase which represents one route of pyroglutamic acid synthesis in the stratum corneum. (see: J G Barrett & I R Scott 1983 "Pyrrolidone carboxylic acid synthesis in guinea pig epidermis." J Invest. Dermatol. 81, 122). It has been discovered that the esters according to the invention readily penetrate into the stratum corneum, and there provide a substrate for this enzyme at the normal site of pyroglutamic acid synthesis, that is, inside the cells of the stratum corneum.

The amount of pyroglutamic acid produced naturally in the stratum corneum is strictly limited by the amount of a preformed protein precursor accumulated by the stratum corneum cell while it is undergoing development (see: I R Scott, C R Harding & J G Barrett (1982) "Histidine-rich protein of the keratohyalin granules : source of free amino acids, urocanic acid and pyrrolidone carboxylic acid in the stratum corneum". Biochim. Biophys-Acta 719, 110). Treatment of the skin with the esters according to the invention can therefore allow the skin to produce, using its own synthetic machinery, higher levels of pyroglutamic acid than would otherwise be possible.

Because pyroglutamic acid is thereby produced within the cells of the stratum corneum, it is very resistant to removal by washing, a significant fraction remaining after a continuous 2 hour period of water washing.

Enzyme action on the esters according to the invention liberates not only pyroglutamic acid but also free alpha-hydroxy acids which also have proven skin benefit properties.

#### QUANTITATIVE DATA ON EFFICACY

In an in vitro laboratory test, ethyl-2-pyroglutamyl propionate labelled with <sup>3</sup>H on the pyroglutamic acid residue was applied as a 1% solution in ethanol to newborn rat skin held in a glass cell, allowing the dermal side of the skin to be bathed in a buffered salts solution while the epidermal surface was exposed to normal atmospheric conditions. At intervals of 24 hours, samples of skin were taken and washed with continuous agitation in several changes of water at room temperature.

Interfollicular epidermis was removed from these skin pieces by "freeze scraping" - which avoids contamination of the sample by follicular tissue or material trapped within the hair follicle. The epidermis was then  
5 extracted in methanol and the soluble extract analysed by thin layer chromatography. The amount of tritiated pyroglutamic acid present was calculated as nmoles/cm<sup>2</sup> of skin surface.

10 The results showed that tritiated pyroglutamic acid was produced from the applied tritiated ethyl-2-pyroglutamyl propionate at a rate of 16 nmoles/cm<sup>2</sup>/day for a period of at least 3 days following the single application. Of the ethyl-2-pyroglutamyl  
15 propionate applied, one quarter was converted into pyroglutamic acid over a 24 hour period, and one third of this pyroglutamic acid resisted the continuous period of 2 hours water washing.

20 The substantivity of tritiated pyroglutamic acid produced by the skin from tritiated ethyl-2-pyroglutamyl propionate was compared with that of tritiated pyroglutamic acid applied directly to the skin and left for the same period of time (24 hours). The percentage  
25 of the tritiated pyroglutamic acid remaining in the skin was measured over a sequence of five 20 minute water washes. The results are shown in Table 1 below:

TABLE 1

5	No. of washes	% pyroglutamic acid remaining in epidermis	
		from ethyl-2-pyroglutamyl propionate applied topically	from pyroglutamic acid applied topically
10	0	100	100
	1	80	20
	2	40	4
	3	36	3
15	4	33	2
	5	31	1

From these results, it can be seen that a substantial amount of pyroglutamic acid remains in the epidermis after repeated washing when that pyroglutamic acid is derived from ethyl-2-pyroglutamyl propionate according to the invention. When free pyroglutamic acid is applied to the epidermis, it is entirely washed from the tissue after a similar number of repeated washings.

25

The procedure described above was repeated with other tritiated esters of pyroglutamic acid according to the invention; these are listed in Table 2 below. In each case, these esters were applied to 1cm<sup>2</sup> of newborn rat skin as 10μl of a 2% solution in ethanol. After 24 hours, the amount of tritiated pyroglutamic acid present in the epidermis in a form resistant to a period of 2 hours continuous washing with water was measured. The quantity of tritiated pyroglutamic acid delivered and retained by the skin in this way is recorded in Table 2 below:

35

TABLE 2

Esters of tritiated pyroglutamic acid applied topically	Tritiated pyroglutamic acid delivered to epidermis : nmoles/cm <sup>2</sup> /day
ethyl-2-pyroglutamyl propionate	25±5
ethyl-2-pyroglutamyl n-valerate	10.5±4
ethyl-2-pyroglutamyl n-caproate	12±4
ethyl-2pyroglutamyl n-caprylate	5±0.5

IN VITRO TESTS ON HUMAN SKIN

Initial experiments carried out on human scalp using a similar methodology to that shown above indicate that the rate of production of substantive tritiated pyroglutamic acid is comparable to that obtained using newborn rat skin, being 11 nmoles/cm<sup>2</sup>/day. The level of naturally occurring pyroglutamic acid in the same samples was measured as 34 nmoles/cm<sup>2</sup>. A period of three days continuous treatment with the ethyl-2-pyroglutamyl propionate can therefore double the naturally occurring level of pyroglutamic acid in the stratum corneum. Since the normal turnover time of human stratum corneum is 2-3 weeks, the stratum corneum is generating pyroglutamic acid five times faster from ethyl-2-pyroglutamyl propionate than it does from its own endogenous pyroglutamic acid precursors. The pyroglutamic acid delivered from the ester should therefore have significant beneficial effects on the moisture binding properties of the skin.

IN VIVO TESTS ON HUMAN SKIN

An in vivo study using human subjects was carried out according to the following procedure.

5

A solution of 5% by weight ethyl-2-pyroglutamyl propionate in 10% ethanol:90% water was applied to the upper arm over the biceps each evening for four days. A control solution of 10% ethanol:90% water was applied to the other arm. The arms were washed each evening before application. After this period of application, the arms were allowed to rest for three days with thorough washing of the arms each day.

15

Sellotape strips were used to sample the superficial stratum corneum on the test sites each day for a further 11 days. The arms were not washed during this period. The pyroglutamic acid content of the tapes strips was measured and expressed as n moles per mg of total protein on the strip, measured by the ninhydrin reaction after acid hydrolysis.

20

The results given in Table 3 below showed an increase of about 50% in the pyroglutamic acid content of the stratum corneum which persists for up to 11 days from the end of treatment. As this represents approximately the normal turnover time of the stratum corneum, the results show that treatment with ethyl-2-pyroglutamyl propionate increases the pyroglutamic acid content throughout the whole stratum corneum and not merely in the superficial layers.

25

30

TABLE 3

Pyroglutamic acid level in tape strip (nmoles/mg protein)			
Days since end of treatment	Test Site	Control Site	Test: Control Ratio
3	145	86	1.69
4	252	165	1.53
5	410	269	1.52
7	322	256	1.26
8	483	312	1.55
10	435	337	1.29
11	370	322	1.15
13	190	233	0.82

A further in vivo study using human subjects was carried out according to the following procedure.

8 volunteers applied a 5% by weight solution of ethyl-2-pyroglutamyl propionate in 10% ethanol:90% water to the back of the hand and upper arm on one side of the body and a control solution of 10% ethanol:90% water to the hand and arm on the other side. Allocation of test and control sides was random, the panellists were not informed which was the test solution.

The applications were made each evening and hands and arms were washed as normal the following day. Treatment continued for 7 days then all treated sites were thoroughly washed.

4 successive tape strips were taken from each treatment site and analysed for pyroglutamic acid and

protein. Pyroglutamic acid was expressed as nmoles/mg total protein as in the previously described in vivo study.

5           Analysis of variance of the results showed that test and control sites differed significantly in pyroglutamic acid level ( $P < 0.001$ ). In the case of the hand, treatment with ethyl-2-pyroglutamyl propionate increased pyroglutamic acid level 1.75 times although there was  
10       variation in this mean value between the different strips taken from any one site. On the arm, the increase was 2.34 times and was fairly consistent from the first to the last strip.

15           Compositions containing esters of the invention are further illustrated by the following Examples of topical compositions suitable for application to human skin.

Example 12

20

This example illustrates a high internal phase water-in-oil emulsion containing an ester of the invention.

25           A high internal phase water-in-oil emulsion having the following formulation was prepared:

	<u>% w/w</u>
Fully hydrogenated coconut oil	3.9
2-pyroglutamyl propionic acid	5
30       Brij 92*	5
Bentone 38	0.5
Preservative	0.3
MgSO <sub>4</sub> 7H <sub>2</sub> O	0.3
Butylated hydroxy toluene	0.01
35       Perfume	qs
Water	to 100
*Brij 92 is polyoxyethylene (2) oleyl ether	

Example 13

This example illustrates an oil-in-water cream containing an ester of the invention.

5

An oil-in-water cream emulsion having the following formulation was prepared:

	<u>% w/w</u>
10	
Mineral oil	4
Ethyl-2-pyroglutamyl propionate	0.1
Brij 56*	4
Alfol 16RD*	4
15	
Triethanolamine	0.75
Butane-1,3-diol	3
Xanthan gum	0.3
Preservative	0.4
Perfume	qs
20	
Butylated hydroxy toluene	0.01
Water	to 100

\*Brij 56 is cetyl alcohol POE (10)  
Alfol 16RD is cetyl alcohol

25

Example 14

This example illustrates an alcoholic lotion containing an ester of the invention.

30

The lotion had the following formulation:

	<u>% w/w</u>
iso-Propyl-2-pyroglutamyl propionate	0.2
Ethanol	40
5 Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

Example 15

10

This example illustrates an alcoholic lotion containing an ester of the invention.

The lotion had the following formulation:

	<u>% w/w</u>
15 Ethyl-2-pyroglutamyl n-caprylate	1
Dimethylsulphoxide	10
Ethanol	40
Antioxidant	0.1
20 Perfume	qs
Water	to 100

Examples 16 & 17

25 The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

	<u>% w/w</u>	
	<u>16</u>	<u>17</u>
30 Glyceryl mono(2-pyroglutamyl propionate)	1.5	-
Stearyl-2-pyroglutamyl stearate	-	0.5
Perfume	0.1	0.1
Hydroxyethyl cellulose	0.4	0.4
35 Absolute ethanol	25	25
p-methyl benzoate	0.2	0.2
Sterilised demineralised water	to 100	100

Examples 18 & 19

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

		<u>% w/w</u>	
		<u>18</u>	<u>19</u>
10	12-hydroxy-stearyl-2-pyroglutamyl stearate	8	-
	Ethyl-2-pyroglutamyl-3-hydroxy n-butyrate	-	15
	Ethanol	10	10
15	Perfume	0.5	0.5
	Distilled water	to 100	100

Examples 20 & 21

The following compositions according to the invention represent creams which can be used to treat skin burns:

		<u>% w/w</u>	
		<u>20</u>	<u>21</u>
25	Methyl-2-pyroglutamyl acetate	3	-
	n-propyl-2-pyroglutamyl n-caprylate	-	2
	Cetyl alcohol	8	8
30	Mineral oil	4	-
	Paraffin wax	-	2
	Xanthan gum	0.3	0.3
	Preservative	0.4	0.4
	Perfume	qs	qs
35	Demineralised water	to 100	100

Example 22

5 This example illustrates a high internal phase water-in-oil emulsion containing an ester of the invention.

A high internal phase water-in-oil emulsion having the following formulation was prepared:

10		<u>% w/w</u>
	Fully hydrogenated coconut oil	3.9
	Ethyl-2-pyroglutamyl n-butyrate	0.5
	Brij 92*	5
	Bentone 38	0.5
15	Preservative	0.3
	MgSO <sub>4</sub> 7H <sub>2</sub> O	0.3
	Butylated hydroxy toluene	0.01
	Perfume	qs
	Water	to 100

20

\*Brij 92 is polyoxyethylene (2) oleyl ether

Example 23

25 This example illustrates an oil-in-water cream containing an ester of the invention.

An oil-in-water cream emulsion having the following formulation was prepared:

30

		<u>% w/w</u>
	Mineral oil	4
	Ethyl-2-pyroglutamyl n-valerate	0.1
5	Brij 56*	4
	Alfol 16RD*	4
	Triethanolamine	0.75
	Butane-1,3-diol	3
	Xanthan gum	0.3
10	Preservative	0.4
	Perfume	qs
	Butylated hydroxy toluene	0.01
	Water	to 100
15	*Brij 56 is cetyl alcohol POE (10) Alfol 16RD is cetyl alcohol	

Example 24

20        This example illustrates an alcoholic lotion  
containing an ester of the invention.

The lotion had the following formulation:

25		<u>% w/w</u>
	iso-Propyl-2-pyroglutamyl n-caprylate	2
	Ethanol	40
30	Perfume	qs
	Butylated hydroxy toluene	0.01
	Water	to 100

Example 25

35        This example illustrates an alcoholic lotion  
containing an ester of the invention.

The lotion had the following formulation:

		<u>% w/w</u>
5	Ethyl-2-pyroglutamyl n-caprolate	0.2
	Dimethylsulphoxide	10
	Ethanol	40
	Antioxidant	0.1
	Perfume	qs
10	Water	to 100

Examples 26 & 27

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

		<u>% w/w</u>	
		<u>26</u>	<u>27</u>
20	Glyceryl di(2-pyroglutamyl propionate)	1.5	-
	Stearyl-2-pyroglutamyl n-caprylate	-	0.5
	Perfume	0.1	0.1
	Hydroxyethyl cellulose	0.4	0.4
25	Absolute ethanol	25	25
	p-methyl benzoate	0.2	0.2
	Sterilised demineralised water	to 100	100

Examples 28 & 29

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

		<u>% w/w</u>	
		<u>28</u>	<u>29</u>
	Stearyl-2-pyroglutamyl		
	propionate	0.08	-
5	n-propyl-2-pyroglutamyl		
	propionate	-	0.15
	Ethanol	10	10
	Perfume	0.5	0.5
10	Distilled water	to 100	100

Examples 30 & 31

The following compositions according to the invention represent creams which can be used to treat skin burns:

		<u>% w/w</u>	
		<u>30</u>	<u>31</u>
	Ethyl-2-pyroglutamyl acetate	3	-
	iso-Propyl-2-pyroglutamyl		
20	n-caprylate	-	2
	Cetyl alcohol	8	8
	Mineral oil	4	-
	Paraffin wax	-	2
	Xanthan gum	0.3	0.3
25	Preservative	0.4	0.4
	Perfume	qs	qs
	Demineralised water	to 100	100

Example 32

30

This example illustrates a high internal phase water-in-oil emulsion containing an ester of the invention.

35

A high internal phase water-in-oil emulsion having the following formulation was prepared:

		<u>% w/w</u>
	Fully hydrogenated coconut oil	3.9
	ethyl-2-pyroglutamyl iso-butyrate	1
	Brij 92*	5
5	Bentone 38	0.5
	Preservative	0.3
	MgSO <sub>4</sub> 7H <sub>2</sub> O	0.3
	Butylated hydroxy toluene	0.01
	Perfume	qs
10	Water	to 100

\*Brij 92 is polyoxyethylene (2) oleyl ether

### Example 33

15

This example illustrates an oil-in-water cream containing an ester of the invention.

20 An oil-in-water cream emulsion having the following formulation was prepared:

		<u>% w/w</u>
	Mineral oil	4
25	Ethyl-2-pyroglutamyl n-pelargonate	5
	Brij 56*	4
	Alfol 16RD*	4
	Triethanolamine	0.75
	Butane-1,3-diol	3
30	Xanthan gum	0.3
	Preservative	0.4
	Perfume	qs
	Butylated hydroxy toluene	0.01
	Water	to 100

35

\*Brij 56 is cetyl alcohol POE (10)  
Alfol 16RD is cetyl alcohol

Example 34

This example illustrates an alcoholic lotion containing an ester of the invention.

5

The lotion had the following formulation:

		<u>% w/w</u>
10	glyceryl mono(2-pyrroglutamyl n-caprylate)	12
	Ethanol	40
	Perfume	qs
	Butylated hydroxy toluene	0.01
15	Water	to 100

Example 35

This example illustrates an alcoholic lotion containing an ester of the invention.

20

The lotion had the following formulation:

		<u>% w/w</u>
25	Palmityl-2-pyrroglutamyl propionate	5
	Dimethylsulphoxide	10
	Ethanol	40
	Antioxidant	0.1
30	Perfume	qs
	Water	to 100

Examples 36 & 37

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

		<u>% w/w</u>	
		<u>36</u>	<u>37</u>
10	Linoleoyl-2-pyroglyutamyl		
	propionate	15	-
	Stearyl-2-pyroglyutamyl stearate	-	10
	Perfume	0.1	0.1
	Hydroxyethyl cellulose	0.4	0.4
15	Absolute ethanol	25	25
	p-methyl benzoate	0.2	0.2
	Sterilised demineralised water	to 100	100

Examples 38 & 39

20

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

		<u>% w/w</u>	
		<u>38</u>	<u>39</u>
25	Linoleoyl-2-pyroglyutamyl		
	n-caprylate	2	-
	Lauryl-2-pyroglyutamyl		
30	n-caprylate	-	3
	Ethanol	10	10
	Perfume	0.5	0.5
	Distilled water	to 100	100

35

Examples 40 & 41

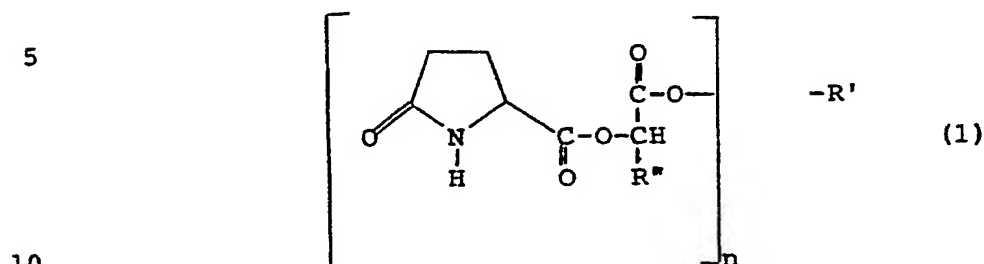
The following compositions according to the invention represent creams which can be used to treat skin burns:

5

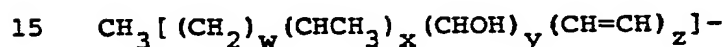
		<u>% w/w</u>	
		<u>40</u>	<u>41</u>
10	Methyl-2-pyroglutamyl		
	n-heptylate	3	-
	ethyl-2-pyroglutamyl		
	n-caprylate	-	2
	Cetyl alcohol	8	8
	Mineral oil	4	-
15	Paraffin wax	-	2
	Xanthan gum	0.3	0.3
	Preservative	0.4	0.4
	Perfume	qs	qs
	Demineralised water	to 100	100

CLAIMS:

1. Esters of pyroglutamic acid having the structure:



where R' and R'' are the same or different and are each represented by H or the grouping



where n is an interger of from 1 to 3

w is zero, or an integer of from 1 to 21

x is zero, or an integer of from 1 to 4

20 y is zero, or an integer of from 1 to 2

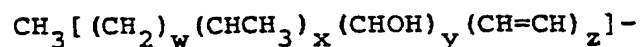
z is zero, or an integer of from 1 to 4

provided that the total number of of carbon atoms in each of said grouping will not exceed 22;

25

and provided also that when the subgrouping (CH=CH) is present, then the total number of carbon atoms in said grouping will be from 16 to 22.

- 30 2. An ester according to claim 1, in which the grouping



is chosen from:

35

methyl

ethyl

propyl  
iso-propyl  
butyl  
iso-butyl  
5 tert-butyl  
valeryl  
iso-valeryl  
caproyl  
heptyl  
10 caprylyl  
capryl  
lauryl  
myristyl  
palmityl  
15 stearyl  
arachidyl  
behenyl  
hydroxy methyl  
2-hydroxy ethyl  
20 2-hydroxy propyl  
3-hydroxy propyl  
2-hydroxy butyl  
3-hydroxy butyl  
4-hydroxy butyl  
25 5-hydroxy valeryl  
6-hydroxy caproyl  
2,3-dihydroxy propyl  
2,3-dihydroxy butyl  
12-hydroxy stearyl  
30 linoleoyl  
linolenoyl, and  
arachidonyl.

3. An ester according to claim 1 or 2 chosen from:  
35 2-pyroglutamyl propionic acid  
methyl-2-pyroglutamyl acetate

ethyl-2-pyroglutamyl propionate  
 ethyl-2-pyroglutamyl n-butyrate  
 ethyl-2-pyroglutamyl iso-butyrate  
 ethyl-2-pyroglutamyl n-valerate  
 5 ethyl-2-pyroglutamyl n-caproate  
 ethyl-2-pyroglutamyl n-heptylate  
 ethyl-2-pyroglutamyl n-caprylate  
 ethyl-2-pyroglutamyl n-pelargonate  
 ethyl-2-pyroglutamyl-3-hydroxybutyrate  
 10 iso-propyl-2-pyroglutamyl propionate  
 iso-propyl-2-pyroglutamyl n-caprylate  
 n-propyl-2-pyroglutamyl propionate  
 n-propyl-2-pyroglutamyl n-caprylate  
 glyceryl mono(2-pyroglutamyl propionate)  
 15 glyceryl di(2-pyroglutamyl propionate)  
 stearyl-2-pyroglutamyl propionate  
 12-hydroxystearyl-2-pyroglutamyl propionate  
 stearyl-2-pyroglutamyl stearate  
 palmityl-2-pyroglutamyl propionate  
 20 linoleoyl-2-pyroglutamyl propionate  
 linoleoyl-2-pyroglutamyl n-caprylate  
 glyceryl mono(2-pyroglutamyl n-caprylate)  
 lauryl-2-pyroglutamyl n-caprylate, and  
 stearyl-2-pyroglutamyl n-caprylate.

25

4. A process for the synthesis of esters of pyroglutamic acid according to claim 1, 2 or 3, which comprises the steps of:

30 (i) reacting pyroglutamic acid with an ester having the structure:

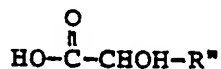


35

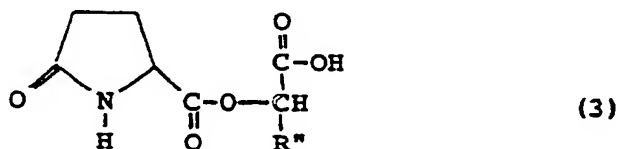
(ii) and isolating the ester of pyroglutamic acid so obtained.

5. A process for the synthesis of esters of pyroglutamic acid according to claim 1, 2 or 3, which comprises the steps of:

- 5 (i) reacting pyroglutamic acid with an alpha hydroxy acid having the structure:



10 to form an ester having the structure:



- 15 (ii) condensing the ester (3) with an alcohol having the structure  
 $\text{R}'\text{OH}$   
 20 (iii) and isolating the ester of pyroglutamic acid so obtained.

6. A process according to claim 4 or 5, in which pyroglutamic acid and the ester are reacted in the presence of a solvent.

7. A process according to claim 4, 5 or 6 in which pyroglutamic acid and the ester are reacted in the presence of a drying agent.

8. A composition for topical treatment to human skin which comprises an effective amount of from 0.01 to 99% by weight of an ester of pyroglutamic acid according to claim 1, 2 or 3, together with a physiologically and cosmetically acceptable diluent.

9. A composition according to claim 8 which further comprises a sunscreen agent.

10. A composition according to claim 8 or 9, which is a  
5 solution, dispersion, gel or cream.



European Patent  
Office

# EUROPEAN SEARCH REPORT

0176217

Application number

EP 85 30 5862

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	CH-A- 591 505 (F. HOFFMANN-LA ROCHE & CO.) * column 1, lines 1-38, example 3 *	1,2	C 07 D 207/28 A 61 K 7/48 A 61 K 31/40
A	--- CHEMICAL ABSTRACTS, vol. 98, no. 9, 28th February 1983, page 331, abstract no. 77945t, Columbus, Ohio, US; & JP - A - 57 91733 (POLA CHEMICAL INDUSTRIES INC.) 08-06-1982	1,8,10	
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A	--- DE-A-2 102 172 (DR. KARL THOMAE GMBH) * page 1, line 1 - page 3, line 4 * -----	1,4,6- 8,10	C 07 D 207/00 A 61 K 7/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 19-11-1985	Examiner VAN AMSTERDAM L.J.P.
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>			